Individual Differences in the Kinetics of Alcohol Absorption and Elimination

A Human Study

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Abstract

The individual differences in alcohol pharmacokinetics were studied using the one-compartment model with first-order absorption and zero-order elimination kinetics in humans. The blood alcohol concentrations (BACs) were simulated by obtained parameters, absorption rate constant (ka), and elimination rate constant (β). The 81 healthy young Japanese volunteers, who had been divided into those without alcohol-induced facial flushing (nonflushers) and those with facial flushing (flushers) according to alcohol patch test results and a questionnaire beforehand, ingested 0.50 g/kg ethanol within 1 minute. Breath alcohol concentrations (BrACs) were measured during absorption and during the elimination period. BACs were obtained based on BrACs. Fifteen percent of subjects exhibited low BAC profile (below 0.4 mg/mL) (first-pass effect [FPE] group), although the majority showed normal BAC profile (normal group). The ka was approximately 5 to 8 (h−1) in the normal group without significant difference between nonflushers and flushers, whereas that in the FPE group was significantly smaller than in the normal group. For the normal group, peak BACs were well simulated by the one-compartment model with first-order absorption and zero-order elimination kinetics. A considerable portion of subjects exhibited FPE. Absorption of alcohol from the intestine plays an important role in alcohol pharmacokinetics in humans.

Key Words: Alcohol pharmacokinetics; absorption rate constant; first-pass effect; human study.

Fig. 1. Blood alcohol concentration (BAC) in the first-pass effect (FPE) group and the normal group with curve-fitting. Open circles (o): FPE in nonflushers (n = 9); filled circles (●): FPE in flushers (n = 3); x: the normal group with curves fitted (n = 51). The BAC in the FPE group remains below 0.4 mg/mL and is lower than that in the normal group (mean ± SD).

The experimental protocol was approved by the Human Research Committee, Kyoto Prefectural University of Medicine (Serial No. HRC-1 and HRC-13). To find flushers, each subject completed a questionnaire and received an alcohol patch test, in which skin redness was observed 10 minutes after contact with 70% alcohol for 7 minutes (5). The subjects then drank 0.5 g/kg body weight of ethanol in the form of whisky (35%) mixed with water (total volume: approximately 100 mL) within 1 minute. None of the subjects revealed severe ill effects, such as vomiting or bad headache.

The experiments began around 2:00 PM, and the subjects had not eaten lunch. We measured breath alcohol concentration (BrAC) every 6 minutes during the absorption–distribution period and every 30 minutes during the elimination period using Alcomed 3010 (EniteC-Wismar GmbH, Wismar, Germany) with a total of 10 to 15 measurements. The apparatus was used in the sampling mode and the subjects breathed directly into the instrument with a mouthpiece tube (6). For the purpose of alleviating experimental overload of subjects, we also collected a blood sample of 29 subjects, during the ethanol elimination period and measured BAC by head-space gas chromatography (2). Through simultaneous measurements of BAC and BrAC, the ratios of BAC to BrAC were calculated (2401 ± 517 [mean ± SD]; Pearson’s correlation coefficient: r = 0.767, n = 29). We used Fisher’s Z-transformation for approximation to the normal distribution [Z = (1/2)ln(1 + r)/(1 – r) = 1.013, Zr = Z(n – 3)/√(2n) = 5.165 > z(0.0001/2) = 3.891; p < 0.0001]. The value of the ratio we obtained is slightly higher than usually reported (2100); the coefficient between the two assays was not so strong. In this experiment, we adopted the ratio (2401) because we obtained the value in the same experimental conditions. We estimated the BAC from noninvasive BrAC. The first-pass effect (FPE) group was defined as those subjects who showed neither clear peaks of BACs nor maximum BAC below 0.4 mg/mL; the other majority (normal group) showed clear peaks of BAC as shown in Fig. 1.

For the normal group, we conducted the following kinetic study. We used a one-compartment model with first-order absorption and zero-order elimination kinetics. The equation used was:

\[ C = \frac{D}{V_d/F} \left[ 1 - e^{-ka \cdot t} \right] - \beta \]  

where: C (mg · mL⁻¹) = BAC; D (g · kg⁻¹) = dose (0.50); ka (h⁻¹) = absorption rate constant; Vd/F (L · kg⁻¹) = distribution volume/bioavailability; \( \beta \) (mg · mL⁻¹ · h⁻¹) = zero-order elimination rate constant.

These parameters were estimated using the weighted nonlinear least-squares method. The estimated initial value was determined via linear regression analysis. The modified Marquardt method was used for curve-fitting as shown previously (7). In these kinetic studies, the computer program MULTI (8) was used on an IBM-compatible microcomputer (FMV Deskpower, Fujitsu, Tokyo, Japan). The numbers of the normal group and the FPE group, or nonflushers and flushers, are shown in Table 1. For kinetic study, nonflushers and flushers in the normal group were analyzed separately. The data of the cases, which are not curve-fitted, were omitted. For the FPE group, ka and \( \beta \) values were estimated using the first-order absorption model and the regression curve, respectively. Data are expressed as the mean ± SD and were analyzed using Student’s unpaired t-test.

**RESULTS**

Sixty-three percent (51/81) of the subjects followed the first-order absorption and zero-order elimination kinetic model (normal group); 22% (18/81) did not, whereas 15% (12/81) showed FPE with a low ka of 2.21 ± 0.76 (FPE group, including both nonflushers and flushers) compared with a ka of 6.65 ± 5.11 in the normal group, including both nonflushers and flushers (Fig. 2A). These FPE group subjects showed lower BACs with their peaks below 0.4 mg/mL (Fig. 1) and were excluded for the curve-fitting studies.

For nonflushers, the mean ka value (Fig. 2A) and the \( \beta \) value (Fig. 2B) in the FPE group was significantly smaller than those in the normal group. To examine the effect of acetaldehyde on the alcohol disposition profile, we then compared the ka and

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**Table 1**

<table>
<thead>
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<th>Total number</th>
<th>Normal or FPE group</th>
<th>Nonflusher or flusher</th>
<th>Curve fitted or not fitted</th>
<th>FPE group 12</th>
<th>Nonflusher 9</th>
<th>Flusher 3</th>
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<tbody>
<tr>
<td>81</td>
<td>Normal group 69</td>
<td>Nonflusher 52</td>
<td>Curve fitted 35</td>
<td>Flusher 17</td>
<td>Curve fitted 16</td>
<td>Noncurve fitted 1</td>
</tr>
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Uemura et al.